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EPPERSON, JON D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/804,481	GRAAF ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-35,39-46 and 48-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35, 39-46, and 48-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed October 30, 2007 response is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 32-35, 37-46 and 48-51 were pending. Applicants canceled claims 37-38 and added claims 52-53. In addition, claims 32, 41, and 42 have been amended. Therefore, claims 32-35, 39-46, and 48-53 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The 35 U.S.C. § 112, second paragraph rejection denoted "A" is withdrawn in view of Applicants' amendment limiting the claim to only one recognition site. The 35 U.S.C. § 112, second paragraph rejection denoted "B" is withdrawn in view of Applicants' arguments (e.g., see 7/12/07 response, page 8). All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 32-35, 39-46, and 48-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants' claims are directed to a broad genus recombinant vectors (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.). In addition, although said vectors must contain a recognition site for a dual cleavage restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (e.g., class I, class II, class IIs, class III, etc).

In contrast, Applicants' specification provides only one example of a pSP-luc+ plasmid contains U1 and a Bael "double cleavage" restriction site i.e., a Bael/U1 construct (e.g., see figure 4; see also Example on pages 21-23).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). Furthermore, adequate disclosure, like enablement, requires representative species, which provide reasonable assurance to one skilled in the art that that applicant had possession of the ***full scope*** of the claimed invention (e.g., see *In re Riat* (CCPA

1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05; see also see *In re Fisher*, 166 USPQ 18 (CCPA 1970)) ("... what the Applicants have actually made and tested [must] reasonably correlate with the scope of the amended claims").

In the present case, Applicants' specification discloses only one example of the claimed genus of recombinant vectors, the Bael/U1 construct, which is not "representative" of this enormous genus (see above). For example, Applicants fail to list representative recombinant vectors (e.g., viral, plasmid, etc.) that can infect representative host cells (e.g., human, bacterial, yeast, etc.) or any representative species of mechanism (e.g., replicate, integrate, etc.). In addition, Applicants fail to list examples of Type I and Type III endonucleases. Applicants also fail to list Type II endonucleases that cleave within the recognition site.

Furthermore, Applicants claims encompass the use of Type I and Type III endonucleases where, in contrast to type II enzymes, there is no "strict control" over the cut site (e.g., see Brown, T. A. Genomes. New York: Wiley, Inc. **1999**, pages 30, "There are three types of restriction endonuclease. With Types I and III there is no strict control over the position of the cut relative to the recognition sequence, but with Type II enzymes the cut is always at the same place, either within the recognition sequence or very close to it"). Therefore, Applicants cannot be in possession of a genus of vectors produced by

Type I/III endonucleases because they cannot predict with certainty where these enzymes will cut as exemplified by Brown.

In addition, a large number of Types I-III restriction enzymes cleave within their own recognition site (e.g., BamHI cleaves G↓GATCC), which would destroy the recognition site. Although the specificity of a restriction enzyme may be changed by mutation and/or judicious selection of reaction conditions (e.g., see George et al., abstract wherein the recognition of BamHI could be "relaxed" by altering the reaction conditions; see also Lanio et al., Table I wherein mutations in EcoRV caused changes in the substrate specificity), no such "relaxation" has been described in Applicants' specification, nor has an alternative procedures (e.g., mutation) been suggested that might otherwise alter the enzymes recognition and/or cleavage sites.

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention especially with regard to sequences that do not possess a restriction site that can be "double cleavage" restriction site. It is well settled that claiming only a result (e.g., digestion with a single enzyme that excises a restriction fragment which includes a single recognition site and forms insertion sites in said nucleotide sequence) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl.

D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that they have amended independent claims 32 and 42 to recite the use of a "dual cleavage" enzyme and thus have overcome the previous rejection (e.g., see 7/12/07 Response, pages 5 and 6, especially page 6, first full paragraph).

[1] The Examiner respectfully disagrees. The "dual cleavage" limitation does not distinguish Types I/III from type II i.e., all three classes possess "dual cleavage" enzymes (e.g., see Brown, T.A. Genomes, New York, Wiley Inc., page 40) (of record). The main difference, according to Brown, is that there is "no strict control" over the "positions" at which the cuts are made relative to the recognition site, not that a different number of cuts are made for each class (see Brown, page 40, paragraph 2). Furthermore, Applicants admit that only Type II enzymes can be used (e.g., see 7/12/07 Response, page 6, third full paragraph, "Although restriction enzymes are traditionally classified into three types, it is known in the art that Type II enzymes are the only class used in the laboratory for DNA analysis and gene cloning since they cut DNA at defined positions close to or

within their recognition sequences and produce discrete restriction fragments" and cite Exhibit A in support of this position. In addition, Type II enzymes that cleave within their recognition sites would not provide a restriction fragment that includes the recognition site upon excision because the recognition site would be cut upon excision. Thus, Applicants have not shown that they are in possession of these vectors since no "relaxation" techniques have been provided that could compensate for these deficiencies.

[2] Applicants argue, "One of skill in the art would know that the claimed invention is useful for the DNA cloning technology and the recited restriction enzyme is a Type II enzyme, rather than a Type I/III enzyme, in light of the teachings of the specification. Applicants have added new dependent claims 52-53 to specify that the restriction is a Type II restriction enzyme" (e.g., 7/12/07 Response, page 6, second to last paragraph).

[2] It is respectfully submitted that the first sentence is logically inconsistent with the second. If one of skill in the art "would know" that the claimed invention was limited to Type II enzymes based on the specification then there would be no need to add dependent claims 52-53 further specifying this limitation. Stated another way, if the independent claims were limited to Type II enzymes as purported then claims 52 and 53 would not further limit these claims. Thus, it is clear that the independent claims are not limited to Type II enzymes as erroneously purported. To the contrary, the doctrine of claim differentiation creates a presumption that each claim in a patent has a different scope. *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187, 48 USPQ2d

1001, 1005 (Fed. Cir. 1998). "There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." Id. at 1005. Thus, claims 52 and 53 only serve to prove the Examiner's point that independent claims 32 and 42 are not limited to Type II enzymes.

[3] Applicants argue, "that where, as in the case, (1) the inventive portion of the subject matter is disclosed and (2) any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that the application was in possession of the genus, the written description cannot be deemed defective" (e.g., see 7/12/07 Response, page 7, paragraphs 1 and 2, especially paragraph 2).

[3] Applicants have already admitted that a person of skill in the art would not recognize that they were in possession of a method using Type I/III enzymes (e.g., see 7/12/07 Response, page 6, third full paragraph, "Although restriction enzymes are traditionally classified into three types, it is known in the art that Type II enzymes are the only class used in the laboratory for DNA analysis and gene cloning since they cut DNA at defined positions close to or within their recognition sequences and produce discrete restriction fragments"). Furthermore, the Examiner has proved using the doctrine of

claim differentiation (see section [2] above) that Applicants' claims encompass such embodiments. Thus, the guidelines support the Examiner's position.

[4] Applicants argue, " Applicants further point out that at the time this application was filed, various splicesome snRNAs ... were known in the art ... Also, various vectors were constructed utilizing snRNAs to deliver antisense targeting sequences" (e.g., see 7/12/07 Response, page 7, last paragraph).

[4] None of these publications speak to the issue of using a Type I/III enzyme, nor do they speak to the use of a Type II enzyme that cleaves within its recognition site and yet somehow still preserves the recognition site after cleavage.

Accordingly, the written description rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 32-35, 39-46, and 48-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Type II restriction enzymes wherein the cuts are made "outside" the recognition site, does not reasonably provide enablement for Type I/III and Type II wherein the cut is made inside the recognition site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some

of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicants' claims are directed to a broad genus recombinant vectors (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.). In addition, although said vectors must contain a recognition site for a restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (e.g., class I, class II, class IIs, class III, etc.). Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Applicants claims encompass the use of Type I and Type III endonucleases that are inherently unpredictable to work with since there is no "strict control" over the cut site (e.g., see Brown, T. A. Genomes. New York: Wiley, Inc. 1999, pages 30, "There are three types of restriction endonuclease. With Types I and III there is no strict control over the position of the cut relative to the recognition sequence, but with Type II enzymes the cut is always at the same place, either within the recognition sequence or very close to it"). In

addition, a person of skill in the art would not expect a "dual cleavage" enzyme to excise a restriction fragment that includes the recognition site if that enzyme cleaves within its own recognition site (e.g., many enzymes like BamHI, which cleaves G↓GATCC see below, would destroy the recognition site, please note that the enzyme also cleaves the other strand and thus could be considered a "dual cleavage" enzyme). Although the specificity of a restriction enzyme may be changed by mutation and/or judicious selection of reaction conditions (e.g., see George et al., abstract wherein the recognition of BamHI could be "relaxed" by altering the reaction conditions; see also Lanio et al., Table I wherein mutations in EcoRV caused changes in the substrate specificity), no such "relaxation" has been described in Applicants' specification, nor has an alternative procedures (e.g., mutation) been suggested that might otherwise alter the enzymes recognition and/or cleavage sites.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants' specification provides only one example of a pSP-luc+ plasmid contains U1 and a Bae1 "double cleavage" restriction site i.e., a Bae1/U1 construct (e.g., see figure 4; see also Example on pages 21-23).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be

great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Response

8. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection might have been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "that one of skill in the art would know that independent claims 32 and 42 relate to Type II, rather than Type I or II, restriction enzymes" (e.g., see 7/12/07 Response, page 9).

[1] The Examiner contends that this issue was adequately addressed in the written description section above. If Applicants want to limit their claims to Type II restriction enzymes they can simply incorporate the subject matter of newly added claims 52 and 53 into these claims.

[2] Applicants argue that they are not required to "test the efficacy of all species of the claimed invention" and cite *In re Angstadt* in support of this position (e.g., see 7/12/07 response, page 19, paragraph 1).

[2] The Examiner has never argued that every species need be tested. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). Here, Applicants claimed encompass Types I/III and type II that cleaves within the recognition site. None of these embodiments are operative. Therefore, Applicants have not taught through illustrative examples or terminology how to make and use the invention as broadly as it in claimed in accordance with *In re Vaeck.*

Accordingly, the Enablement rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102/103

9. Claims 32-34, 37-46 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Verhasselt et al. (Verhasselt et al., "Sequence Analysis of a 37·6 kbp Cosmid Clone from the Right Arm of Saccharomyces cerevisiae Chromosome XII" *Yeast* **1998**, *13*, 241–250) as evidenced by Sears et al. (Sears et al. "BaeI, another unusual BcgI-like restriction endonuclease" *Nucleic Acids Research* **1996**, *24*, 18, 3590-3592) and Genomenet (Genomenet, Database: EMBL-today Entry: X89514. Retrieved from http://www.genome.jp/dbget-bin/www_bget?embl-today+X89514 on 12/22/06, pages 1-17).

For ***claim 32***, Verhasselt et al. (see entire document) disclose a 37.6 kbp cosmid vector from the right arm of saccharomyces cerevisiae chromosome XII carrying snR6 (see title and abstract), which anticipates the claimed invention. For example, Verhasselt et al. disclose a recombinant vector (e.g., see figure 1 showing "cosmid" cloning vector) comprising an isolated nucleotide sequence encoding an snRNA (e.g., see title wherein snR6 is disclosed; see also page 246, column 1, paragraph 1) wherein said snRNA-encoding nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme such that digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector (e.g., see Verhasselt et al., figure 1, see also abstract disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874 wherein Y = C and NNNN = CCAG; see also Sears, abstract disclosing the ACNNNNGTAYC

binding motif for BaeI). Furthermore, according to Sears et al., restriction with a BaeI enzyme would cleave 10/15 and 12/7 residues to each side (i.e., a "dual" cleavage enzyme, see also 35 U.S.C. § 112, second paragraph rejection below) of the ACNNNNGTAYC recognition site thus releasing the recognition site upon cleavage by a single enzyme.

The 37.6 kbp cosmid disclosed by Verhasselt et al. meet all of the structural limitations of the claimed product (see above) except for the product-by-process limitations (i.e., the "digesting" method step) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a recombinant vector (i.e., a product), but are defined by various method steps (i.e., digestion method steps) that distinguish said vector from other vectors and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was synthesized and/or prepared.

Alternatively, that this limitation is inherently disclosed. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical

chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Here, the 37.6 kbp cosmid contains a BaeI recognition sequence and thus should release the BaeI recognition site upon cleavage with only a single enzyme because BaeI cleaves on both sides of the recognition site as evidenced by Sears et al. (e.g., see Sears et al., abstract).

For ***claims 33 and 34***, Verhasselt et al. disclose U6 snRNA (e.g., see paragraph bridging pages 243 and 246, "The 37 649 kbp contain ... the SNR6 gene for the small nuclear RNA U6").

For ***claim 37***, Verhasselt et al. disclose a nucleotide sequence that contains two recognition sites that are identical (e.g., see Genomemet, page 11, positions 15415-15425 wherein another identical ACNNNNGTAYC site is disclosed).

For ***claims 38 and 39***, Verhasselt et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Verhasselt et al., figure 1, see also abstract disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874

wherein Y = C and NNNN = CCAG at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 40***, Verhasselt et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 11749-11753 and 1046-1050 (e.g., see Genomenet, pages 10 and 8), respectively.

For ***claim 41***, Verhasselt et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Verhasselt et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 42***, Verhasselt et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding an snRNA (e.g., see above wherein U6 snRNA is disclosed) wherein said nucleotide sequence comprises an insertion cassette between two insertion sites (e.g., see Verhasselt et al., abstract wherein 25 open reading frames are disclosed between two "flanking" cosmid insertion sites). The method limitation to form

by digestion with a single restriction enzyme to excise from said vector a restriction fragment that contains a recognition site for said restriction enzyme and wherein said insertion cassette comprises a modification fragment comprising a nucleotide sequence complementary to a target" has not been afforded any patentable weight because as noted above "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, an enzyme like BaeI would not impart any "structural difference" to the sequence because it cleaves 10/15 and 12/7 nucleotides from the ACNNNNGTAYC sequence. Thus, "any" sequence could be produced by this cut because the cut does not depend on the identity of the nucleotides 10/15 and 12/7 nucleotides away from the 5' and 3' ends of the ACNNNNGTAYC sequence. Likewise, the identity of the modification fragment also encompasses "any" sequence because the target to which it binds has not been specified. In addition, the metes and bound of the claimed invention cannot be determined because it is unclear what constitutes a cassette (e.g., see 35 U.S.C. 112, second paragraph rejection above).

For ***claims 43-45***, Verhasselt et al. disclose U6 snRNA (e.g., see paragraph bridging pages 243 and 246, "The 37 649 kbp contain ... the SNR6 gene for the small nuclear RNA U6").

For ***claims 46, 48***, Verhasselt et al. disclose an insertion cassette comprises a modification fragment of about 30 base pairs of DNA (e.g., any 30 bp segment of the 36 639 bp cosmid clone qualifies, see above). Furthermore, the cosmid clone is double

stranded, which reads on claim 48.

For ***claim 49***, Verhasselt et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Verhasselt et al., figure 1, see also abstract disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874 wherein Y = C and NNNN = CCAG at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 50***, Verhasselt et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 11749-11753 and 1046-1050 (e.g., see Genomenet, pages 10 and 8), respectively.

For ***claim 51***, Verhasselt et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Verhasselt et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Response

10. Applicant's arguments directed to the above 35 U.S.C. §§ 102/103 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection might have been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Verhasselt et al. disclose ... a BaeI recognition site [that] is located at positions 5864-5874 ... which is outside the snRNA-encoding gene" (e.g., see 7/12/07 Response, pages 10 and 11, especially page 11, first full paragraph) and, as a result, the Verhasselt et al. reference does not anticipate/render obvious the currently amended claims that add the "snRNA-encoding" limitation to both independent claims.

[1] The Examiner respectfully disagrees. The "snRNA-encoding" limitation has not altered the scope of the claims. The previous limitation (i.e., "said nucleotide sequence") referred to the same sequence as currently claimed (i.e., "said snRNA-encoding nucleotide sequence"). That is, Applicants have not limited the scope of the claims to include a recognition site within the snRNA-encoding "portion" of the snRNA-encoding sequence as purported. For example, claim 24 doesn't read, "A recombinant vector comprising an isolated nucleotide sequence encoding an snRNA, wherein the snRNA-encoding portion of said snRNA-encoding nucleotide sequence has been modified to contain a recognition site." Thus, Applicants' arguments are moot. Please also note that Applicants define the "snRNA-encoding nucleotide

sequence" using "comprising" open-ended language that would not limit the sequence to just the snRNA-encoding portion.

[2] Applicants argue, "In addition, Verhasselt et al. do not teach that the snRNA-encoding gene ... has been modified to contain a recognition site ... [or] has been modified to comprise an insertion cassette between two insertion sites as recited in claim 32 or 42" (e.g., see 7/12/07 Response, page 11, second to last paragraph).

[2] As noted in the above rejection, the patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, the method for producing the product (i.e., with respect to the "has been modified" limitation) has not been set forth in the claims. The claims merely state that the sequence was modified without specifying anything about the nature of that modification. Thus, there is no basis for establishing a "structural difference" between the claimed vectors and those made by the undefined method set forth in the claims.

[3] Applicants argue that Verhasselt et al. do not teach all of the limitations in the claim again and that Verhasselt et al. does not provide a motivation to alter the teachings to obtain such limitations (e.g., see 7/12/07 Response, pages 11 and 12).

[3] It is respectfully submitted that Verhasselt et al. teach all the limitations as set forth in the rejection and arguments above. Consequently, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102/103 rejection cited above is maintained.

11. Claims 32-35, 38-46 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shambaugh et al. (Shambaugh et al., "The splicesomal U small nuclear RNAs of Ascaris lumbricoides" *Molecular and Biochemical Parasitology* **1994**, *64*, 349-352) as evidenced by Sears et al. (Sears et al. "BaeI, another unusual BcgI-like restriction endonuclease" Nucleic Acids Research 1996, **24**, 18, 3590-3592) and NCBI (NCBI, Entry: L22246. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nucleotide&val=L22246 on 12/23/06, pages 1-3).

For ***claim 32***, Shambaugh et al. (see entire document) disclose a 6 kb restrict fragment containing four U1 genes (see Shambaugh et al., page 350, column 1, first full paragraph; see also figure 1; see also page 349, Note at bottom disclosing L22246 accession number), which anticipates the claimed invention. For example, Shambaugh et al. disclose a recombinant vector (e.g., see page 350, column 1, first full paragraph) comprising an isolated nucleotide sequence encoding an snRNA (e.g., see page 350, column 1, first full paragraph wherein U1 snRNA is disclosed; see also NCBI, page 1) wherein said nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme such that digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector (e.g., see Shambaugh et al., page 349, disclosing L22246 accession number; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for

BaeI). Furthermore, according to Sears et al., restriction with a BaeI enzyme would cleave 10/15 and 12/7 residues to each side of the ACNNNNGTAYC recognition site thus releasing the recognition site upon cleavage by a single enzyme.

The L22246 clone meets all of the structural limitations of the claimed product (see above) except for the product-by-process limitations (i.e., the "digesting" method step) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a recombinant vector (i.e., a product), but are defined by various method steps (i.e., digestion method steps) that distinguish said vector from other vectors and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was synthesized and/or prepared.

Alternatively, that this limitation is inherently disclosed. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Here, the L22246 clone contains a BaeI recognition sequence and thus should release the BaeI recognition site upon cleavage with only a single enzyme because BaeI cleaves on both sides of the recognition site as evidenced by Sears et al. (e.g., see Sears et al., abstract).

For ***claims 33 and 34***, Shambaugh et al. disclose U1 snRNA (e.g., see page 350, column 1, first full paragraph; see also NCBI, page 1).

For ***claim 35***, Shambaugh et al. disclose a vector wherein the snRNA is U1 and wherein said nucleotide sequence has been modified within the first 11 nucleotides of the coding region (e.g., see NCBI, page 1 wherein four U1 snRNAs are disclosed with different modification in the first 11 nucleotides of the coding region at positions 2071-2236, 3195-3358, 4551-4715, and 5535-5700. As noted above, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, any U1 snRNA represents a "modification" relative to the other snRNAs because they do not share the same

sequences. Any "method steps" for making a modification are not afforded any patentable weight in accordance with MPEP § 2113 because Applicants are not claiming a method but, rather, a product and "the patentability of a product does not depend on its method of production" as noted above.

For ***claims 38 and 39***, Shambaugh et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Shambaugh et al., page 349, disclosing, L22246; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears et al., abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 40***, Shambaugh et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 3340-3344 and 4343-4347 (e.g., see NCBI, 2 and 3), respectively.

For ***claim 41***, Shambaugh et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Shambaugh et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants

to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 42***, Shambaugh et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding an snRNA (e.g., see above wherein U6 snRNA is disclosed) wherein said nucleotide sequence comprises an insertion cassette between two insertion sites (e.g., see Shambaugh et al., page 350, column 1, first full paragraph wherein any and/or all of the U1 genes represent the insertion cassette i.e., the whole 6 kb is a restriction fragment). The method limitation to form by "digestion with a single restriction enzyme to excise from said vector a restriction fragment that contains a recognition site for said restriction enzyme and wherein said insertion cassette comprises a modification fragment comprising a nucleotide sequence complementary to a target" has not been afforded any patentable weight because as noted above "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, an enzyme like BaeI would not impart any "structural difference" to the sequence because it cleaves 10/15 and 12/7 nucleotides from the ACNNNNGTAYC sequence. Thus, "any" sequence could be produced by this cut because the cut does not depend on the identity of the nucleotides 10/15 and 12/7 nucleotides away from the 5' and 3' ends of the ACNNNNGTAYC sequence. Likewise, the identity of the modification fragment also encompasses "any" sequence because the target to which it binds has not been specified. In addition, the

metes and bound of the claimed invention cannot be determined because it is unclear what constitutes a cassette (e.g., see 35 U.S.C. 112, second paragraph rejection above).

For ***claims 43-45***, Shambaugh et al. disclose U1 snRNA (e.g., see page 350, column 1, first full paragraph; see also NCBI accession L22246).

For ***claims 46, 48***, Shambaugh et al. disclose an insertion cassette comprises a modification fragment of about 30 base pairs of DNA (e.g., see figure 1 wherein any 30 bp segment qualifies, see above; see also NCBI, wherein any 30 base pair segment qualifies). Furthermore, note that 6 kb restrict fragment is double stranded, which reads on claim 48.

For ***claim 49***, Shambaugh et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see page 349, disclosing, L22246; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears et al., abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 50***, Shambaugh et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 3340-3344 and 4343-4347 (e.g., see NCBI, 2 and 3), respectively.

For ***claim 51***, Shambaugh et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Shambaugh et al. (see above) because BaeI produces "3'

overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Response

12. Applicant's arguments directed to the above 35 U.S.C. §§ 102/103 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection might have been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Shambaugh et al. disclose ... a BaeI recognition site ... outside any of the four U1 snRNA-encoding genes" (e.g., see 7/12/07 Response, pages 12, second to last paragraph) and, as a result, the Sambaugh et al. reference does not anticipate/render obvious the currently amended claims that add the "snRNA-encoding" limitation to both independent claims.

[1] The Examiner respectfully disagrees. The "snRNA-encoding" limitation has not altered the scope of the claims. The previous limitation (i.e., "said nucleotide sequence") referred to the same sequence as currently claimed (i.e., said snRNA-encoding nucleotide

sequence). That is, Applicants have not limited the scope of the claims to include a recognition site within the snRNA-encoding "portion" of the snRNA-encoding sequence as purported. For example, claim 24 doesn't read, "A recombinant vector comprising an isolated nucleotide sequence encoding an snRNA, wherein the snRNA-encoding portion of said snRNA-encoding nucleotide sequence has been modified to contain a recognition site." Thus, Applicants' arguments are moot.

[2] Applicants argue, "In addition, Shambaugh et al. do not teach that the snRNA-encoding gene ... has been modified to contain a recognition site ... [or] has been modified to comprise an insertion cassette between two insertion sites as recited in claim 32 or 42" (e.g., see 7/12/07 Response, page 12, last paragraph).

[2] As noted in the above rejection, the patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, the method for producing the product (i.e., with respect to the "has been modified" limitation) has not been set forth in the claims. The claims merely state that the sequence was modified without specifying anything about the nature of that modification. Thus, there is no basis for establishing a "structural difference" between the claimed vectors and those made by the undefined method set forth in the claims. Consequently, Applicants' arguments are moot.

[3] Applicants argue that Shambaugh et al. do not teach all of the limitations in the claim again and that Verhasselt et al. does not provide a motivation to alter the teachings to obtain such limitations (e.g., see 7.12.07 Response, page 13).

[3] It is respectfully submitted that Shambaugh et al. teach all the limitations as set forth in the rejection and arguments above. Consequently, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102/103 rejection cited above is maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639